## REMARKS

Claims 1-5, 7-9, 17-19 and 21-29 are pending. Claims 4, 5 and 17-19 are withdrawn from consideration. Claims 30 and 31 have been added and depend from claims 1 and 21, respectively. The new claims are supported throughout the specification, e.g., paragraphs [0011] and [0043] and Example 1 (paragraphs [0056] to [0058]). Thus, the amendments herein do not introduce any new matter.

Claims 1-3, 7-9 and 21-29 stand rejected as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse as detailed below.

Specifically, the Office Action states that the "specification is not enabling for the claimed antibodies wherein they are 'de-immunized' as per the definition of said term in the specification." Further, the Office Action cites Conry et al. (*Cancer Research* 52, 6979-6982 (1992)) for its alleged disclosure that "the HAMA response to a xenogeneic antibody can occur independent of T cell epitopes on said antibody (eg. preexisting cross reactive antibodies)."

As the Examiner appreciates, the specification defines the term "de-immunization." For example, at paragraph [0036], the specification teaches: "De-immunization renders the anti-CD3 antibody non-immunogenic, or less immunogenic, to a given species." Further, at paragraph [0012], the specification provides:

> In the method which has been termed "de-immunization" and is described herein, amino acids within the antibody sequence that are predicted to bind effectively to HLA molecules are changed such that they no longer bind HLA and thus can no longer stimulate a T cell response. The lack of a T cell response to antigen translates into *a reduction or elimination* of a HAMA response. (emphasis added)

Accordingly, a de-immunized antibody as taught in the instant application encompasses antibodies that are less immunogenic as well as nonimmunogenic.

The Conry et al. reference teaches that the 5 HAMA positive normal patients had no prior exposure to mouse immunoglobulin and demonstrated a lack of memory T-cell responses to mouse

IgG. The preexisting HAMA appears to be specific for mouse constant region and the product of inadvertent cross-reactivity with mouse immunoglobulin by antibodies directed against other antigens. This reference also teaches the 5 HAMA positive normal patients have memory T-cell responses to SLO, "an antigen to which most humans have a memory T-cell response," and concludes that the memory T cells in these patients are not impaired. *See* Fig. 2 of Conry et al.

Accordingly, while the HAMA in those 5 patients in Conry et al. may not have a memory T –cell response to a mouse constant region, the reference teaches that the memory T cells in those patients are not impaired and remain responsive to other antigens (e.g., SLO). Therefore, even if the claimed antibodies include a mouse constant region that would cross-react with HAMA in those 5 patients, the claimed antibodies would still be "de-immunized" (i.e., less immunogenic), if the antibodies before being de-immunized as taught in the claims (as well as the specification) would have triggered a memory T cell response.

Further, the specification provides detailed teaching on how to de-immunize antibodies, e.g., an anti-CD3 antibody. *See, e.g.*, EXAMPLE 1. The specification also teaches that the de-immunized antibodies retain antigen (e.g., CD3) specificity. *See* paragraphs [0091] and [0092]. While de-immunization may result in altered antigen binding strength, the specification provides detailed teachings on how to evaluate the de-immunized antibodies to select those that demonstrate comparable binding to the antigen as the initial antibody (before being de-immunized).

Accordingly, applicants maintain that no undue experimentation is necessary to make the de-immunized antibodies as claimed. As of the filing date, one of ordinary skill could readily follow the steps as taught in the specification to make de-immunized antibodies from an initial antibody. He could then easily employ various routine assays known in the art to determine various structural and/or functional characteristics of the de-immunized antibodies and select those with the desired properties. He could also determine whether such de-immunized antibodies indeed result in a reduced or elimination of a memory T-cell response, for example, by using the routine assays taught in Conry et al. (published in 1992). While the skilled artisan may need to experiment with various de-immunized antibodies, the instant application provides sufficient teachings for making the de-

immunized antibodies, and further testing the de-immunized antibodies to obtain those with desired properties would require no more than routine experimentation. Therefore, Applicants maintain that the pending claims are fully enabled and respectfully request withdrawal of this rejection.

The Office Action also indicates that the Examiner has not considered the IDS (including 3 references) filed by applicants on February 20, 2009 because it allegedly lacks the necessary fee or statement as required. As noted by applicants in the Supplemental Information Disclosure Statement, the three references had been submitted to the Office on June 16, 2006. The February 20, 2009 filing was to submit a copy of the non-patent literature and did not include any new references. While applicants believed that no fee was due with the re-submission on February 20, 2009, the Director was authorized to charge any deficiency in the fees filed. Therefore, if a fee had been required for that re-submission, such a charge would have been authorized already. Accordingly, applicants respectfully submit that the SIDS submitted on February 20, 2009 was in compliance with 37 CFR 1.98 and request that the Examiner consider these three references.

In view of the above amendment and remarks, applicants believe the pending application is in condition for allowance. Applicants believe that no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 18-1945, under Order No. ALXN-P01-106 from which the undersigned is authorized to draw.

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Respectfully submitted,

By_____/Xuqiong Wu/_____

Xuqiong Wu, Ph.D., J.D.
Registration No.: 55,745
ROPES & GRAY LLP
Prudential Tower
800 Boylston Street
Boston, MA 02199-3600
(617) 951-7000
(617) 951-7050 (Fax)
Attorneys/Agents For Applicant